

# **HIV**

## **Human immunodeficiency virus**

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# Introduction

- **Human immunodeficiency virus, is the cause of acquired immunity deficiency disease (AIDS ).**
  - **HIV is present in blood, semen, and other body fluids.**
  - **HIV destroys CD4 lymphocytes resulting in impairment of cell mediated immunity with subsequent susceptibility to opportunistic infections.**
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# Epidemiology

- The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981.
  - The earliest documented case of HIV infection has been traced to a blood sample from the Democratic Republic of Congo in 1959.
  - AIDS is caused by the human immunodeficiency virus (HIV), which progressively impairs cellular immunity.
- 
- The origin of HIV is a zoonotic infection with simian immunodeficiency viruses (SIV) from African primates, probably first infecting local hunters.

# Epidemiology

- **HIV-1 was transmitted from chimpanzees and HIV-2 from sooty mangabey monkeys.**
  - **HIV-1 is the cause of the global HIV pandemic.**
  - **HIV-2, which causes a similar illness to HIV-1 but progresses more slowly and is less transmissible, is restricted mainly to western Africa.**
- 
- **Both HIV-1 and HIV-2 first infected humans about 100 years ago.**

# Epidemiology

- **Three groups of HIV-1, representing three separate transmission events from chimpanzees:**
  - ✓ **M ('major', worldwide distribution).**
  - ✓ **O ('outlier').**
  - ✓ **N ('non-major and non-outlier').**
- **Groups O and N are restricted to West Africa.**
- **Group M consists of nine subtypes: A–D, F–H, J and K.**

# Epidemiology

- **Subtype C (which predominates in sub-Saharan Africa and India) accounts for half of infections and appears to be more readily transmitted.**
- **Subtype B predominates in Western Europe, the Americas and Australia.**
- **In Europe, the prevalence of non-B subtypes is increasing because of migration.**
- **Subtypes A and D are associated with slower and faster disease progression, respectively.**
- **In 2015 it was estimated that there were 36.7 million people living with HIV/AIDS, 2.1 million new infections and 1.1 million AIDS-related deaths.**

# **Modes of transmission**

- **HIV is transmitted by;-**
  - ✓ **sexual contact.**
  - ✓ **Exposure to blood (e.g. injection drug use, occupational exposure in health-care workers).**
  - ✓ **Exposure to blood products.**
  - ✓ **To infants of HIV-infected mothers (who may be infected in utero, perinatally or via breastfeeding).**

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- **Worldwide, the major route of transmission is heterosexual.**

# **Modes of transmission**

- **The risk of contracting HIV after exposure to infected body fluid is dependent on;**
  - **The integrity of the exposed site.**
  - **The type and volume of fluid.**
  - **The level of viremia in the source person.**
- **Risk of HIV transmission reach to 90% after single exposure to an HIV-infected blood transfusion.**

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- **A high proportion of patients with hemophilia in high-income countries had been infected through contaminated blood products by the time HIV antibody screening was adopted in 1985.**

# Modes of transmission

- **Routine screening of blood and blood products for HIV infection has virtually eliminated this as a mode of transmission.**
  - **Because of the lack of adequate screening facilities in resource-poor countries, 5–10% of blood transfusions globally are with HIV-infected blood.**
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# Modes of transmission

Factors that increase the risk of transmission are listed :

Common to all transmission categories	
○ High viral load	
Sexual transmission	
○ STIs, especially genital ulcers.	○ Uncircumcised male partner.
○ Cervical ectopy.	○ Receptive anal intercourse.
○ Rectal or vaginal lacerations.	○ Depot intramuscular progesterone contraceptive use
○ Menstruation	
Injection drug use transmission	
○ Sharing equipment	○ Concomitant cocaine use
○ Linked commercial sex	○ Incarceration
○ Intravenous use	
Occupational transmission	
○ Deep injury	○ Needle was in a blood vessel
○ Visible blood on device	
Vertical transmission	
○ Prolonged rupture of membranes	○ Older gestational age

# Diagnosis

## ❖ Clinical manifestations

- Clinical staging of patients should be done at the initial medical examination.
  - Provides prognostic information and is a key criterion for initiating prophylaxis against opportunistic infections.
- ⇒ The patient with HIV may present with symptoms and signs of any the stage of HIV infection.
- 
- ⇒ No physical finding are specific for HIV infection.
- ⇒ Stages of HIV infections ; 3 stages

# Diagnosis

## ❖ Clinical manifestations

### 1/ Acute conversion stage:- *Primary HIV infection*

- Primary infection is symptomatic in more than 50% of cases but the diagnosis is often missed.
  - The incubation period is usually 2–4 weeks after exposure.
- 
- The duration of symptoms is variable but is seldom longer than 2 weeks.

# Diagnosis

## ❖ Clinical manifestations

### 1/ Acute conversion stage:- *Primary HIV infection*

- The clinical manifestations resemble those of infectious mononucleosis/glandular Fever.
  - The presence of maculopapular rash or mucosal ulceration strongly suggests primary HIV infection rather than the other viral causes.
- 
- Atypical lymphocytosis occurs less frequently than in EBV infection.

# Diagnosis

## ❖ Clinical manifestations

### 1/ Acute conversion stage:- *Primary HIV infection*

- Transient lymphopenia, including CD4 lymphocytes, is found in most cases, which may result in opportunistic infections, notably oropharyngeal candidiasis.
- Major opportunistic infections like *Pneumocystis jirovecii* pneumonia (PJP) may rarely occur.
- Thrombocytopenia and moderate elevation of liver enzymes are commonly present.

# Diagnosis

## ❖ Clinical manifestations

### 1/ Acute conversion stage:- *Primary HIV infection*

#### ➤ The differential diagnosis of primary HIV includes:-

- Acute EBV.
- Primary CMV infection.
- Rubella.
- Primary toxoplasmosis.
- Secondary syphilis.

# Diagnosis

## ❖ Clinical manifestations

### 1/ Acute conversion stage:- *Primary HIV infection*

- Early diagnosis is made by detecting HIV RNA by PCR or antigenemia.
  - The appearance of specific anti-HIV antibodies in serum (seroconversion) occurs 2–12 weeks after the development of symptoms.
- 
- The window period during which antibody tests may be false negative is prolonged when post-exposure prophylaxis has been used.

# Diagnosis

## ❖ Clinical manifestations

### 2/ The asymptomatic stage :-

- Few or no signs or symptoms for a few years to decade or more.
- Generalized benign, commonly characterized by generalized lymphadenopathy.
- During this stage , if untreated, the viral load tends to persist at steady state, but the CD4 T-cells count declines.
- The median time from infection to the development of AIDS in adults is about 9 years

# Diagnosis

## ❖ Clinical manifestations

### 3/ AIDS stage :-

- Manifests as recurrent, severe and occasionally life threatening infection or opportunistic malignancies.
- This manifestation developed when the immune system is damaged.

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### ➤ Note :-

In general all patients remain at risk for Opportunistic infection and of treatment other AIDS related events for the first 6 months .

# Diagnosis

## ❖ Clinical manifestations

- HIV itself is associated All body systems can be affected by HIV.
- The CD4 count is useful in differential diagnosis.
- opportunistic diseases that may present at higher CD4 counts become increasingly common as CD4 counts decline, so the CD4 count helps to rule out certain disorders.

# Diagnosis

## ❖ Clinical manifestations

- For example, in a patient with a pulmonary infiltrate and a CD4 count of 350 cells/mm<sup>3</sup>, pulmonary tuberculosis is a likely diagnosis and PJP is very unlikely, but if the patient's CD4 count is 50 cells/mm<sup>3</sup>, both PJP and tuberculosis are likely.
- Globally, tuberculosis is the most common cause of morbidity and mortality in HIV-infected patients.
- Tuberculosis should be considered in the differential diagnosis of most presenting problems in patients from communities where tuberculosis is common.

# Diagnosis

## ❖ Clinical manifestations

### ❖ CD count and risk of common HIV-associated diseases

#### < 500 cells/mm<sup>3</sup>

- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>○ Tuberculosis</li><li>○ Bacterial pneumonia</li><li>○ Herpes zoster</li><li>○ Oropharyngeal candidiasis</li><li>○ Non-typhoid salmonellosis</li></ul> | <ul style="list-style-type: none"><li>○ Kaposi's sarcoma</li><li>○ Non-Hodgkin lymphoma</li><li>○ HIV-associated idiopathic thrombocytopenic purpura</li></ul> |
|--|--|

#### < 200 cells/mm<sup>3</sup>

- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>○ <i>Pneumocystis jirovecii</i> pneumonia</li><li>○ Chronic herpes simplex ulcers</li><li>○ Oesophageal candidiasis</li><li>○ <i>Cystoisospora belli</i> diarrhoea</li></ul> | <ul style="list-style-type: none"><li>○ HIV-wasting syndrome</li><li>○ HIV-associated dementia</li><li>○ Peripheral neuropathy</li><li>○ Endemic mycoses</li></ul> |
|--|--|

#### < 100 cells/mm<sup>3</sup>

- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>○ Cerebral toxoplasmosis</li><li>○ Cryptococcal meningitis</li><li>○ Cryptosporidiosis and microsporidiosis</li><li>○ Primary CNS lymphoma</li></ul> | <ul style="list-style-type: none"><li>○ Cytomegalovirus</li><li>○ Disseminated <i>Mycobacterium avium</i> complex (MAC)</li><li>○ Progressive multifocal Leucoencephalopathy</li></ul> |
|--|--|

# Diagnosis

## ❖ Clinical manifestations

### ➤ Lymphadenopathy

- ✓ Persistent generalized lymphadenopathy due to HIV in asymptomatic infection.
  - ✓ Lymphadenopathy may also be due to malignancy (Kaposi's sarcoma or lymphoma) or infections, especially tuberculosis.
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- ✓ Tuberculous lymph nodes are often matted and may become fluctuant.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Lymphadenopathy

- ✓ Symmetrical generalized lymphadenopathy may occur in disseminated tuberculosis.
  - ✓ Lymphoma typically presents with large, firm, asymmetric nodes.
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- ✓ Rapid enlargement of a node, asymmetric enlargement or lymphadenopathy associated with constitutional symptoms (even if the nodes are symmetrical) warrants further investigation

# Diagnosis

## ❖ Clinical manifestations

### ➤ Weight loss

- ✓ Weight loss is a very common finding in advanced HIV infection.
  - ✓ The HIV wasting syndrome is an AIDS-defining condition and is defined as weight loss of more than 10% of body weight, plus either unexplained chronic diarrhea (lasting over 1 month) or chronic weakness and unexplained prolonged fever (lasting over 1 month).
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- ✓ This is a diagnosis of exclusion.
  - ✓ If the weight loss is rapid (more than 1 kg a month), then major opportunistic infections or cancers become more likely.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Weight loss

- ✓ Painful oral conditions and nausea from drugs contribute by limiting intake.
- ✓ Depression is very common and can cause significant weight loss.
- ✓ Measurement of C-reactive protein is helpful in the work-up of weight loss, as this is markedly raised with most opportunistic diseases but not with HIV itself.
- ✓ Erythrocyte sedimentation rate (ESR) is elevated by HIV infection and is therefore not useful.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Fever

- ✓ Fever is a very common presenting feature.
- ✓ Common causes of prolonged fever with weight loss are;
  - Non-typhoid *Salmonella* bacteremia.
  - Pyrexia of unknown origin (PUO).
  - HIV can present with prolonged fever.
  - Tuberculosis.
- disseminated *Mycobacterium avium*.
- Disseminated endemic mycoses (e.g. histoplasmosis, coccidioidomycosis, Talaromyces)

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

- ✓ The skin and mouth must be carefully examined, as mucocutaneous manifestations are extremely common in HIV and many prognostically important conditions can be diagnosed by simple inspection.
- ✓ Common dermatological diseases, includes ;-

### ❑ Seborrheic dermatitis

- ✓ Seborrheic dermatitis is very common in HIV.
- ✓ The severity increases as the CD4 count falls.
- ✓ Fungal infections are play a role in the pathogenesis of this condition.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Herpes simplex infections

- ✓ Recurrences of herpes simplex infection are very common.
- ✓ Primarily affect the nasolabial and anogenital areas.
- ✓ As immune suppression worsens, the ulcers take longer to heal and become more extensive.
- ✓ Ulcers that persist for more than 4 weeks are AIDS-defining.
- ✓ Frequent relapses that persist despite ART should be treated with acyclovir 400 mg for 6–12 months.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Herpes zoster

- ✓ Usually presents with a pathognomonic vesicular rash on an erythematous base in a dermatomal distribution.
- ✓ The median CD4 count at the first episode of zoster is 350 cells/mm<sup>3</sup>.
- ✓ The rash may be multi-dermatomal and recurrent episodes may occur.
- ✓ Disseminated zoster is rare.
- ✓ In HIV-infected patients, zoster is generally more extensive and has a longer duration, and there is a higher risk of developing post-herpetic neuralgia.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Kaposi's sarcoma

- ✓ Kaposi's sarcoma (KS) is a spindle-cell tumour of lympho-endothelial origin.
- ✓ All forms of KS are due to sexually transmitted human herpesvirus 8.
- ✓ KS occurs in four patterns:
  - *Classic KS.*
  - *Endemic KS.*
  - *KS in patients on immunosuppressant drugs: usually transplant recipients.*
  - *AIDS-associated KS.*

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Bacillary angiomatosis

- ✓ Is a bacterial infection caused by *Bartonella henselae* or *B. quintana*.
- ✓ Skin lesions range from solitary superficial red–purple lesions resembling KS or pyogenic granuloma, to multiple subcutaneous nodules or plaques.
- ✓ Lesions are painful and may bleed or ulcerate.
- ✓ The infection may become disseminated with fevers, lymphadenopathy and hepatosplenomegaly.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Papular pruritic eruption

- ✓ Papular pruritic eruption is an intensely itchy, symmetrical rash affecting the trunk and extremities.
- ✓ It due to an allergic reaction to insect bites.
- ✓ Post-inflammatory hyperpigmentation is common.

#### ☐ Nail disorders

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- ✓ Fungal infections (onychomycosis, are very common and often involve multiple nails.
- ✓ Blue–black discoloration of nails is common and may be due to HIV or to the antiretroviral drug zidovudine.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Drug rashes

- ✓ Cutaneous hypersensitivity to drugs is said to occur 100 times more frequently in HIV infection.
- ✓ The most common type is an erythematous maculopapular rash.
- ✓ The drugs most commonly associated with rashes are  
Sulphonamides and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Drug rashes

- ✓ Severe, life-threatening features of drug rashes include blistering, involvement of mucous membranes (Stevens–Johnson syndrome, and or systemic involvement with fever or organ dysfunction.
- ✓ Sulphonamides are important in the treatment and prophylaxis of opportunistic infections, rechallenge or desensitisation is often attempted in patients who have previously experienced rashes, provided the reaction was not life-threatening.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Oral conditions

- ✓ Oropharyngeal candidiasis is very common.
- ✓ Pseudomembranous candidiasis is the most common manifestation, with white patches on the buccal mucosa.
- ✓ Erythematous candidiasis is more difficult to diagnose and presents with a reddened mucosa and a smooth shiny tongue.
- ✓ Angular cheilitis due to *Candida* is a common manifestation.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Mucocutaneous diseases

#### ☐ Oral conditions

- ✓ Oral hairy leucoplakia appears as corrugated white plaques running vertically on the side of the tongue and is virtually pathognomonic of HIV disease.
- ✓ Oral ulcers are common.
- ✓ KS often involves the mouth, especially the hard palate.
- ✓ Nodular oral lesions are associated with a worse prognosis.
- ✓ Gingivitis is very common.

# Diagnosis

## ❖ Clinical manifestations

### ➤ GIT diseases

### ☐ Oesophageal diseases

- ✓ Oesophageal candidiasis is the most common cause of pain on swallowing (odynophagia), dysphagia and regurgitation.
  - ✓ Concomitant oral candidiasis is present in about 70% of patients.
- 
- ✓ Major aphthous ulceration and CMV ulcers are the most likely causes, Occasionally, herpes simplex oesophagitis or KS is responsible.

# Diagnosis

## ❖ Clinical manifestations

### ➤ GIT diseases

#### □ Diarrhoea

- ✓ Chronic diarrhoea is a very common presenting problem in patients with advanced HIV.
  - ✓ It is a major cause of wasting.
- 
- ✓ The presentation and etiology of acute diarrhoea are similar to those in HIV-uninfected patients.

# Diagnosis

## ❖ Clinical manifestations

### ➤ GIT diseases

### ☐ Hepatobiliary

- ✓ Chronic viral hepatitis Hepatitis B and/or C (HBV and HCV) co-infection is common in HIV-infected people due to shared risk factors for transmission.
- ✓ Chronic liver disease from viral hepatitis has emerged as a major cause of morbidity and mortality.
- ✓ HIV co-infection with viral hepatitis increases viremia, and increases the risk of liver fibrosis and hepatocellular carcinoma.
- ✓ A flare of hepatitis may be associated with improved immune function after starting ART or discontinuing.
- ✓ HIV co-infection with viral hepatitis increases the risk of antiretroviral hepatotoxicity.

# Diagnosis

## ❖ Clinical manifestations

### ➤ GIT diseases

#### ❑ HIV cholangiopathy

- ✓ HIV cholangiopathy, a form of secondary sclerosing cholangitis.
- ✓ In some patients, coexisting intestinal infection with CMV, cryptosporidiosis or microsporidiosis is present.
- ✓ Papillary stenosis is common.
- ✓ Acalculous cholecystitis is a common complication of cholangiopathy.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Respiratory disease

- ✓ Pulmonary disease is very common and is the major reason for hospital admission.
- ✓ Most patients who are admitted for respiratory diseases will have either bacterial pneumonia, pulmonary tuberculosis or PJP.
- ✓ PJP is more common in high income countries, while tuberculosis is more common in low- and middle-income countries.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Respiratory disease

#### ☐ *Pneumocystis jirovecii* pneumonia

- ✓ The key presenting feature of *Pneumocystis jirovecii* pneumonia (PJP) is progressive dyspnoea with a duration of less than 12 weeks.
- ✓ Dry cough and fever are common.
- ✓ The chest X-ray typically shows a bilateral interstitial infiltrate spreading out from the hilar regions, but may be normal initially.
- ✓ High-resolution CT scan is more sensitive than chest X-ray, usually showing typical 'ground-glass' interstitial infiltrates.
- ✓ Pneumatocoeles may occur and may rupture, resulting in a pneumothorax.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Respiratory disease

#### ☐ Pulmonary tuberculosis

- ✓ In patients with CD4 counts below 200 cells/mm<sup>3</sup>.
- Progresses more rapidly, with a subacute or even acute presentation.
- The chest X-ray appearance alters: cavities are rarely seen, pulmonary infiltrates are no longer predominantly in apical areas, and pleural effusions and hilar or mediastinal lymphadenopathy are common.
- Many patients have disseminated tuberculosis, but more commonly presenting with pulmonary infiltrates together with extrapulmonary tuberculosis.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Respiratory disease

#### ☐ Bacterial pneumonia

- ✓ The incidence of bacterial pneumonia is increased about 100-fold by HIV infection.
- ✓ The severity, bacteraemia, risk of recurrent pneumonia, and mortality are all increased compared with HIV-uninfected patients.
- ✓ The a etiology is similar to that of community-acquired pneumonia in HIV-uninfected patients.
- ✓ The prevalence of atypical bacteria in HIV-infected patients with pneumonia is similar to that in the general population.
- ✓ Uncommon bacteria causing pneumonia include *Pseudomonas aeruginosa*, *Nocardia* (which mimics tuberculosis) and *Rhodococcus equi* (which can cause pulmonary cavities).

# Diagnosis

## ❖ Clinical manifestations

### ➤ Respiratory disease

### ❑ Miscellaneous causes of pulmonary infiltrates

✓ Pulmonary cryptococcosis.

✓ The disseminated endemic mycoses (histoplasmosis, coccidioidomycosis and talaromycosis).

✓ Lymphoid interstitial pneumonitis.

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✓ KS often spreads to the lungs.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Nervous system disease

- ✓ The central and peripheral nervous systems are commonly involved in HIV, either as;
    - A direct consequence of HIV infection.
    - Due to opportunistic diseases.
  - ❑ Cognitive impairment.
- 
- ❑ *Progressive multifocal leukoencephalopathy.*
  - ❑ *CMV encephalitis.*

# Diagnosis

## ❖ Clinical manifestations

### ➤ Nervous system and disease

#### ☐ Space-occupying lesions:-

- *Cerebral toxoplasmosis.*
- *Primary CNS lymphoma.*
- *Tuberculoma.*

#### ☐ Stroke.

#### ☐ Meningitis :-

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- *Cryptococcal meningitis.*
- *Tuberculous meningitis*

# Diagnosis

## ❖ Clinical manifestations

### ➤ Nervous system disease

### ☐ Peripheral nerve disease

- ✓ Sensorimotor peripheral neuropathy in about one-third of patients.
- ✓ The incidence increases with lower CD4 counts, older age and increased height.
- ✓ Sensory symptoms predominate.
- ✓ The NRTIs stavudine and didanosine, can cause drug-induced peripheral neuropathy, which is typically more painful and more rapidly progressive than HIV neuropathy.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Nervous system disease

### ☐ Peripheral nerve disease

- ✓ Acute inflammatory demyelinating polyneuropathy is an uncommon manifestation.
- ✓ Mononeuritis may also occur, commonly involving the facial nerve.
- ✓ Myelopathy and radiculopathy.
- ✓ The most common cause of myelopathy in HIV infection is cord compression from tuberculous spondylitis.

# Diagnosis

## ❖ Clinical manifestations

### ➤ eye disease

#### □ Retinopathy

- ✓ CMV retinitis presents with painless, progressive visual loss in patients with severe immune suppression.
- ✓ The disease usually starts unilaterally but progressive bilateral.
- ✓ May develop immune recovery uveitis in response to ART.
  
- ✓ Three other conditions may mimic CMV retinitis:
  - ocular toxoplasmosis.
  - HIV retinopathy.
  - Varicella zoster virus.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Psychiatric disease

- ✓ Significant psychiatric morbidity is very common.
- ✓ Is a major risk factor for poor adherence.
- ✓ Reactive depression is the most common disorder.
- ✓ Diagnosis is often difficult.
- ✓ Some antiretroviral drugs can cause psychiatric adverse effects.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Rheumatological disease:-

- ✓ Mild arthralgias and a fibromyalgia-like syndrome are common in HIV-infected people.

### ➤ Hematological abnormalities

- ✓ Disorders of all three major cell lines may occur in HIV.
- ✓ In advanced disease, haematopoiesis is impaired due to the direct effect of HIV and by cytokines.
- ✓ Pancytopenia may occur as a consequence of HIV but it is important to exclude a disorder infiltrating the bone marrow.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Hematological abnormalities

#### ☐ Anaemia

- ✓ Normochromic, normocytic anemia is very common in advanced HIV disease.
- ✓ Opportunistic diseases may cause Anaemia of chronic disease.
- ✓ Anaemia is a common adverse effect of zidovudine, which also causes a macrocytosis.
- ✓ Red cell aplasia is rare. may be caused either by parvovirus B19 infection or by lamivudine.

# Diagnosis

## ❖ Clinical manifestations

### ☐ Neutropenia

- ✓ Isolated neutropenia is occasionally due to HIV but is nearly always caused by drug toxicity.

### ☐ Thrombocytopenia

- ✓ Mild thrombocytopenia is common in HIV-infected people.
- ✓ Transient thrombocytopenia is frequently found in primary infection.
- ✓ The most common disorder causing severe thrombocytopenia is immune-mediated platelet destruction resembling idiopathic thrombocytopenic purpura.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Renal disease

- ✓ AKI is common, usually due to acute infection or nephrotoxicity of drugs.
  - ✓ HIV-associated nephropathy is the most important cause of chronic kidney disease.
- 
- ✓ Progression to end-stage disease is more rapid than with most other causes of CKD, and renal size is usually preserved.

# Diagnosis

## ❖ Clinical manifestations

### ➤ Cardiac disease

- ✓ HIV-associated cardiomyopathy resembles idiopathic dilated cardiomyopathy but progresses more rapidly.
- ✓ ART may improve cardiac failure but does not reverse established cardiomyopathy.
- ✓ Pericardial disease due to opportunistic diseases is not uncommon.
- ✓ Globally, the most common cause is tuberculous pericardial effusions.
- ✓ KS and lymphoma may cause pericardial effusions.
- ✓ HIV is associated with an increased risk of myocardial infarction due to atherogenesis.

# Diagnosis

## ❖ Clinical manifestations

### ➤ HIV related cancers

✓ The AIDS-defining cancers are:-

- KS.
- Cervical cancer.
- Non-Hodgkin lymphoma.

✓ NHL may occur at any CD4 count but is more commonly seen with counts below 200 cells/mm<sup>3</sup>.

# Diagnosis

## ❖ Investigations

### ❖ Serological tests :-

- The most important studies in diagnosis of HIV infection.
- If Ag positive Confirmation of HIV AB by ELLISA antibody testing, that to differentiate HIV1 and HIV2, that is faster than the Western blot
- Most tests detect antibodies to both HIV-1 and HIV-2.
- A positive antibody test from two different immunoassays is sufficient to confirm infection.
- Screening tests often include an assay for antigen in addition to antibodies, in order to detect patients with primary infection before the antibody response occurs.

# Diagnosis

## ❖ Investigations

### ❖ Nucleic acid amplification tests (PCR):-

- To detect HIV RNA are used to diagnose infections in infants of HIV-infected mothers.
  - Diagnose primary infection before antibodies have developed.
- 
- More sensitive antigen detection for diagnosing primary infection.

# Diagnosis

## ❖ Investigations

### ❖ *CD4 counts*

- CD4 counts are usually determined by flow cytometry.
- Is the most clinically useful laboratory indicator of the degree of immune suppression; it is used, together with clinical staging, in decisions to start prophylaxis against opportunistic infections.
- The CD4 count varies by up to 20% from day to day and is also transiently reduced by intercurrent infections.
- Due to this variability, major therapeutic decisions should not be taken on the basis of a single count.

# Diagnosis

## ❖ Investigations

### ❖ *CD4 counts*

- The normal CD4 count is over 500 cells/mm.
- People with CD4 counts between 200 and 500 cells/mm<sup>3</sup> have a low risk of developing major opportunistic infections.
- Morbidity becomes increasingly common as CD4 counts decline.
- The count is below 200 cells/mm<sup>3</sup>, there is severe immune suppression and a high risk of AIDS-defining conditions.
- The CD4 count should be performed every 3–6 months in patients on ART, together with measurement of the viral load

# Diagnosis

## ❖ Investigations

### ❖ *Viral load*

- The level of viremia is measured by quantitative PCR of HIV RNA, known as the viral load.
- The viral load is crucial for monitoring responses to ART.
- People with high viral loads (e.g.  $> 100\,000$  copies/mL) experience more rapid declines in CD4 count.
- while those with low viral loads ( $< 1000$  copies/mL) usually have slow or even no decline in CD4 counts.
- Viral loads are variable; only changes in viral load of more than  $0.5 \log_{10}$  copies/mL are considered clinically significant.

# Diagnosis

## ❖ Investigations

### ❖ Baseline studies for other infection that includes :-

- PPD skin testing for TB.
- Cytomegalovirus testing.
- Syphilis testing.
- Rapid amplification testing for gonococcal and chlamydial infection.
- Hepatitis A, B, C virus.
- Anti-toxoplasmosis

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⇒ Baseline values of factors that may be affected by ART include the following :

L.F.T, serum chemistry, R.F.T, lipid panel, Vit B12, Folic acid, and T.F.T.

# Management

## ❖ Prevention of opportunistic infections

- **The best way to prevent opportunistic infections is to improve the CD4 count with ART.**
- **However, infections continue to occur in the ART as CD4 counts take time to improve if;**
  - **ART is initiated in patients with profound immune suppression.**
  - **Immune reconstitution on ART is often suboptimal.**
  - **CD4 counts may decline because antiretroviral resistance develops.**

# Management

## ❖ Prevention of opportunistic infections

### ○ Preventing exposure

- The best method for avoiding infection is to prevent exposure to the infectious agent.
- This is possible only for a few opportunistic infections.
- Many opportunistic infections occur after reactivation of latent/dormant infection after prior exposure.

### ☐ Safe water and food

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### ☐ Tuberculosis

### ☐ Malaria vector control

### ☐ Safer sex

### ☐ Pets

# Management

## ❖ Prevention of opportunistic infections

### ○ Chemoprophylaxis

- ✓ The use of antimicrobial agents to prevent infections.
- ✓ Primary prophylaxis is used to prevent opportunistic infections that have not yet occurred.
- ✓ Secondary prophylaxis is used to prevent recurrence of opportunistic infections because many may recur after an initial response to therapy.
- ✓ Secondary prophylaxis can be discontinued when;
  - ART results in immune reconstitution, with CD4 counts increasing to over 200 cells/mm<sup>3</sup>.
  - Stopped if CD4 counts increase to more than 100 cells/mm<sup>3</sup> for CMV and MAC.

# Management

## ❖ Prevention of opportunistic infections

### ❑ Co-trimoxazole primary prophylaxis

- ✓ Reduces the incidence of a number of opportunistic infections, resulting in lower hospitalization and mortality rates.
- ✓ The indications for initiating co-trimoxazole are either clinical evidence of immune suppression (WHO clinical stages 3 or 4) or laboratory evidence of immune suppression (CD4 count  $< 200$  cells/mm<sup>3</sup>).
- ✓ The recommended dose of co-trimoxazole is 960 mg daily.
- ✓ Can be discontinued when CD4 counts increase to more than 200 cells/mm<sup>3</sup> on ART, except in low-income countries where it should be continued life-long.

# Management

## ❖ Prevention of opportunistic infections

### ❑ Co-trimoxazole primary prophylaxis

✓ Co-trimoxazole prophylaxis is well tolerated.

✓ If co-trimoxazole cannot be tolerated, then dapsone 100 mg daily should be substituted.

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✓ Dapsone is equally effective only at reducing the incidence of *P. jirovecii* pneumonia.

# Management

## ❖ Prevention of opportunistic infections

### ➤ Opportunistic infections reduced by co-trimoxazole

✓ Pneumocystis jirovecii pneumonia

✓ Cerebral toxoplasmosis

✓ Bacterial pneumonia

✓ Bacteremia

✓ Cystoisosporiasis

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✓ Malaria

# Management

## ❖ Prevention of opportunistic infections

### ❑ Tuberculosis preventive therapy

- ✓ That preventive therapy, either with isoniazid or combinations of rifamycin with isoniazid, reduces the risk of tuberculosis only in HIV-infected patients with a positive tuberculin skin test.
- ✓ In HIV infection, induration of 5 mm or more on a Mantoux test is regarded as positive.
- ✓ No CD4 count or clinical threshold for starting or stopping tuberculosis preventive therapy.

# Management

## ❖ Prevention of opportunistic infections

### ❑ Tuberculosis preventive therapy

- ✓ Important to rule out active tuberculosis before starting preventive therapy.
- ✓ The usual duration of isoniazid preventive therapy is 6 months but this does not provide long-term reduction in the risk of tuberculosis.
- ✓ Isoniazid for 36 months has more effective in people with a positive tuberculin skin test.
- ✓ Rifampicin or rifapentine combined with isoniazid for 12 weeks has been shown to be at least as effective as 6–12 months of isoniazid.

# Management

## ❖ Prevention of opportunistic infections

### ❑ *Mycobacterium avium* complex prophylaxis

- ✓ In high-income countries a macrolide (azithromycin or clarithromycin) is recommended to prevent MAC in patients with a CD4 count below 50 cells/mm<sup>3</sup>.
- ✓ Can be discontinued once the CD4 count has risen to over 100 cells/mm<sup>3</sup> on ART.
- ✓ MAC is uncommon in low- and middle-income countries and primary prophylaxis is thus not warranted.

### ❑ Preventing cryptococcosis

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- ✓ Serum cryptococcal antigen test should be done in patients with a CD4 count below 100 cells/mm<sup>3</sup>.
- ✓ If positive, pre-emptive therapy with fluconazole should be commenced.

# Management

## ❖ Prevention of opportunistic infections

### ○ Immunization

➤ The following additional vaccines are also recommended:

- *hepatitis A*: in those at risk.
- *human papillomavirus*: in people < 40 years old.
- *measles, mumps and rubella (MMR)*: in those with negative measles serology.
- *meningococcus*: in people < 25 years old, those with asplenia or complement deficiency, during outbreaks.

# Management

## ❖ Prevention of opportunistic infections

### ○ Immunization

➤ The following additional vaccines are also recommended:

○ *diphtheria/tetanus/acellular pertussis (dTaP)/inactivated poliovirus vaccine (IPV)*: meeting general indications.

○ *chickenpox*: if seronegative; those who are seropositive should receive the shingles vaccine.

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○ Bacille Calmette–Guérin (BCG) is contraindicated in all HIV-infected people.

# Management

## ❖ Antiretroviral therapy

- ART has transformed HIV from a progressive illness with a fatal outcome into a chronic manageable disease with a near-normal life expectancy.
- The goals of ART are to:
  - Reduce the viral load to an undetectable level for as long as possible.
  - Improve the CD4 count to over 200 cells/mm<sup>3</sup> so that severe HIV-related disease is unlikely.
  - Improve the quantity and quality of life without unacceptable drug toxicity.
  - Reduce HIV transmission.

# Management

## ❖ Antiretroviral therapy

## ❖ Guidelines on the timing of initiating of ART are as the following :-

⇒ ART reduce morbidity and mortality and prevent transmission.

⇒ Initiating ART immediately or as soon possible after diagnosis.

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⇒ Important to educate patients regarding the benefits of ART, when initiating ART.

# Management

## ❖ Antiretroviral therapy

### ❖ Guidelines on the timing of initiating of ART are as the following :-

- ⇒ Initiating Art is important in patients with AIDS defining condition, patient with acute or current infection and pregnancy patient.
- ⇒ HIV patients with ART should be informed that monitoring replication ( viral load < 200 Copies/ml ) prevents sexual transmission to their partners.
- ⇒ Highly active ART ( HAART ) is the principle method for preventing immune deterioration.

# Management

## ❖ Antiretroviral therapy

### ❑ Selecting antiretroviral regimens

- The standard combination antiretroviral regimens are two NRTIs together with an NNRTI, protease inhibitor (PI) or integrase inhibitor.
  - Most guidelines from high-income countries, allow clinicians to choose a starting regimen of dual NRTIs combined with an NNRTI, or a PI or an integrase inhibitor, as these three regimens have similar efficacy.
- 
- Subsequent ART regimen switches for virological failure are guided by the results of resistance testing.
  - For low- and middle-income countries, the WHO recommends to using ART with standardized first-line (NNRTI plus dual NRTIs) and second-line (ritonavir-boosted PI plus dual NRTIs) regimens.

# Management

## ❖ Antiretroviral therapy

### ❑ Selecting antiretroviral regimens

- NNRTIs are preferred by the WHO in first-line regimens, as they are cheaper than PIs and better tolerated.
  - NNRTIs need to be given with two fully active NRTIs because they have a low genetic barrier to resistance, whereas PI-containing regimens are effective even when there are some mutations conferring resistance to the NRTIs.
- 
- PIs in second-line regimens are therefore preferable in settings where resistance testing is not widely available.

# Management

## ❖ Antiretroviral therapy

### ❑ Monitoring efficacy

- The most important measure of ART efficacy is the viral load.
  - A baseline viral load should be measured prior to initiating treatment.
  - Viral load measurement should be repeated 4 weeks after starting ART, when there should be at least a 10-fold decrease.
- 
- The viral load should be suppressed after 6 months.
  - Once the viral load is suppressed, measurement should be repeated 6-monthly.

# Management

## ❖ Antiretroviral therapy

### ☐ Monitoring efficacy

- Failure of ART is defined by the viral load becoming detectable after suppression.
  - A viral load threshold is used to define virological failure, e.g. more than 200 (UK) or more than 1000 (WHO) copies/mL.
- 
- Adherence support should be enhanced if virological failure is detected, and measurement of the viral load repeated to confirm failure before switching to a new ART regimen.

# Management

## ❖ Antiretroviral therapy

### ☐ Monitoring efficacy

- CD4 counts are generally monitored every 6 months together with the viral load, but there is little point in repeating the CD4 count in patients who maintain virological suppression and whose CD4 count is  $> 350$  cells/mm<sup>3</sup>.
  - The CD4 count increases rapidly in the first month, followed by a more gradual increase.
- 
- In the first year, the CD4 count typically increases by 100–150 cells/mm<sup>3</sup>, and about 80 cells/mm<sup>3</sup> per annum thereafter until the reference range is reached, provided the viral load is suppressed.

# Management

## ❖ Antiretroviral therapy

### ❑ Antiretroviral resistance

- If ART is taken and there is ongoing replication, due to either resistant mutations or suboptimal adherence, mutations conferring resistance to antiretroviral drugs will be selected.
  - Some drugs (e.g. emtricitabine, lamivudine, efavirenz) have a low genetic barrier to resistance, rapidly selecting for a single mutation conferring high-level resistance.
- 
- PIs and some NRTIs (e.g. zidovudine) select for resistance mutations slowly, and multiple resistant mutations often need to accumulate before the drug's efficacy is lost.

# Management

## ❖ Antiretroviral therapy

### ☐ ART complications

#### ➤ Immune reconstitution inflammatory syndrome

- ✓ Is a common early complication of ART, especially in patients who start ART with CD4 counts below 50 cells/mm<sup>3</sup>.
- ✓ Presents either with paradoxical deterioration of an existing opportunistic disease or with the unmasking of a new infection.
- ✓ The clinical presentation is often characterized by an exaggerated immune response, with pronounced inflammatory features.
- ✓ IRIS is associated with a mortality of around 5% but this is higher when it complicates CNS infections.

# Management

## ❖ Antiretroviral therapy

### ☐ ART complications

#### ➤ Immune reconstitution inflammatory syndrome

- ✓ The management of IRIS is to continue ART and to ensure that the opportunistic disease is adequately treated.
- ✓ Symptomatic treatments are helpful.
- ✓ Glucocorticoids are often used for more severe IRIS manifestations but they should not be given to patients with KS, as this can result in rapid progression of KS lesions.

# Management

## ❖ Antiretroviral therapy

### ☐ ART complications

#### ➤ Lipodystrophy

- ✓ Long-term use of ART is associated with changes in body fat distribution called lipodystrophy.
- ✓ The thymidine analogue NRTIs are associated with fat loss.
- ✓ Switching to the non-thymidine NRTIs, abacavir or tenofovir, will result in very gradual improvement of lipoatrophy.
- ✓ All classes of antiretrovirals are associated with fat gain to a similar extent.

# Management

## ❖ Antiretroviral therapy

### ❑ ART complications

#### ➤ Hypersensitivity rashes

- ✓ Are common but must be differentiated from the other causes.
- ✓ The NRTI abacavir typically causes a systemic hypersensitivity reaction, which is limited to people with HLA-B\*5701.
- ✓ Re-challenge must never be attempted after abacavir hypersensitivity, as fatal reactions may occur.

# Management

## ❖ Antiretroviral therapy

### ❑ ART complications

#### ➤ Drug rashes:-

- ✓ Are very common with NNRTIs.
- ✓ When the NNRTI rash is mild and not accompanied by systemic involvement, the suspected drug is often continued and antihistamines are administered.
- ✓ The rash usually resolves.
- ✓ If it worsens or if systemic features develop, the NNRTI should be discontinued.

# Management

## ❖ Antiretroviral therapy

### ☐ ART complications

#### ➤ Other adverse effects

- ✓ The NNRTI efavirenz causes insomnia, agitation, euphoria or dysphoria in many patients but tolerance to its neuropsychiatric effects develops in a few weeks in most patients.
- ✓ The NRTI zidovudine can cause Anaemia and neutropenia, and tenofovir may cause nephrotoxicity and loss of bone mineral density.
- ✓ Some PIs are associated with dyslipidemias and may increase the risk of myocardial infarction.

# Management

## ❖ Antiretroviral therapy

### ☐ ART in special situations

#### ○ Pregnancy

- All pregnant women should have HIV testing at an early stage in pregnancy.
- The CD4 count falls by about 25% during pregnancy due to hemodilution.
- The course of HIV disease progression is not altered by pregnancy.
- In the pre-ART, the rate of mother-to-child transmission was 15–40%.
- ART has dramatically reduced the risk of mother-to-child transmission of HIV to less than 1%.

# Management

## ❖ Antiretroviral therapy

### ☐ ART in special situations

#### ○ Pregnancy

- All pregnant women should start ART at the beginning of the second trimester, unless they have advanced disease, when ART should be started in the first trimester.
- Caesarean section is associated with a lower risk of mother to-child transmission than vaginal delivery, but the mode of delivery does not affect transmission risk if the viral load is suppressed on ART.
- HIV is also transmitted by breastfeeding.

# Management

## ❖ Antiretroviral therapy

### □ ART in special situations

#### ○ Pregnancy

- The minimal risk of transmitting HIV by breastfeeding in women with a suppressed viral load on ART.
  - Providing antiretrovirals to infants (usually nevirapine monotherapy) while they are breastfeeding has been shown to reduce the risk of transmission.
- 
- Breastfeeding is therefore now encouraged in resource-poor settings.

# Management

## ❖ Antiretroviral therapy

### ☐ ART in special situations

#### ○ Pregnancy

- **Diagnosis of HIV in infancy requires the detection of HIV RNA by PCR, as maternal antibodies to HIV, which persist for up to 15 months, will give a false-positive result on antibody assays.**
  - **PCR should ideally be carried out within 6 weeks of birth to facilitate early ART initiation.**
- 
- **If the baby is breastfed, the PCR should be repeated 2 weeks after weaning.**

# Management

## ❖ Prevention of HIV

➤ Measures for the prevention of HIV transmission are shown in:-

### ❖ Sexual

- Sex education programmes in schools
- Easily accessible voluntary counselling and testing centres
- Promotion of safer sex practices (delaying sexual debut, condom use, fewer sexual partners)
- Effective ART for HIV-infected individuals
- Pre-exposure prophylaxis for high-risk groups
- Male circumcision
- Post-exposure prophylaxis

### ❖ Parenteral

- Blood product transmission: donor questionnaire, routine screening of donated blood
- Injection drug use: education, needle/syringe exchange, avoidance of 'shooting galleries', methadone maintenance programmes

### ❖ Occupational

- Education/training: universal precautions, needlestick injury avoidance
- Post-exposure prophylaxis

### ❖ Perinatal

- Routine 'opt-out' antenatal HIV antibody testing
- Measures to reduce vertical transmission (see text)

# Management

## ❖ Prevention of HIV

### □ Pre-exposure prophylaxis

- **(PrEP) with daily tenofovir plus emtricitabine has been shown to reduce the risk of HIV acquisition in people at ongoing high risk (e.g. from sex or injecting drug use) and is well tolerated.**
  - **Regular HIV testing should be done in people on PrEP.**
-

# Management

## ❖ Prevention of HIV

### ❑ Post-exposure prophylaxis

- (PEP) is recommended when the risk is deemed to be significant after a careful risk assessment.
- The first dose should be given as soon as possible, preferably within 6–8 hours.
- No point in starting PEP after 72 hours.
- Tenofovir together with emtricitabine is the most widely used dual NRTI combination, together with either a PI or an integrase inhibitor.
- PEP should not be given if the exposed person is HIV-infected.
- HIV antibody testing should be performed at 3 months after exposure.

# Thank you